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Review Article

## A Review on New Trends in Preparation of Long Acting Microspheres

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### ABSTRACT

The Purpose of designing sustained or controlled delivery systems has always been to bring down the dose frequency that offers better patient compliance & reduced side effects. Microspheres have shown to reduce the dose, side effects, frequency of administration and possibility of dose dumping, therefore increased patient compliance. There are several methods of preparation for microspheres, slight variation in basic method can produce numerous changes in final outcome. However various problems are still not resolved with these methods like wide size distribution & poor repeatability. Biodegradation rate of the microspheres is controlled by the composition of the microspheres and consecutively affects the release profile of drug, i.e. PGA, PLA and PCL have hydrolytic degradation role in order of PGA>PLA>>PCL.

**Keywords:** controlled delivery, microspheres, patient compliance

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### INTRODUCTION

The purpose of designing sustained or controlled delivery systems has always been to improve pharmacokinetic profile of a drug candidate viz. extended half-life, improved bioavailability with reduction in dosing frequency. In addition, this system also offers target site delivery, better patient compliance, reduces frequency and severity particularly in the case of cytotoxic drugs where one intends to achieve only local or target specific action<sup>(1)</sup>. Among many available drug delivery systems for sustained release of the drug microspheres is gaining world-wide popularity due to high efficiency and better compatibility. Biodegradable polymers have been approved by US FDA and are widely employed in surgical sutures, implantable devices and in drug delivery systems. Microspheres as delivery systems have shown improved outcome via alteration of release profile of various drugs, proteins and genes.

Microspheres have now been considered as reliable and effective release system which reduces dose, dosing frequency, and possibility of dose dumping with high patient compliance<sup>(2)</sup>. Microspheres prepared by innate or artificial polymers provides sustained release, for instance polyesters used in microspheres, have the benefit of using water as a vehicle to form suspensions which offers constant release of desired drug. It has been documented

that release of a drug from microsphere is directly influenced with certain factors viz. physicochemical properties of a drug, primary burst and excipients<sup>3</sup>.

Injectable microsphere systems were developed in late 70's. Poly (lactide) and/or poly (lactide-co-glycolide) was used to encapsulate an ester of norethisteron called NET via oil-in-water emulsion/solvent evaporation process. These microcrystals of NET were encapsulated into microspheres of PLA and PLGA. Since then PLGA has been the first choice of polymer for preparation of microspheres to encapsulate APIs using w/o or o/w emulsion/solvent evaporation technique. Poly (ε-caprolactone) is the secondly most accepted polymer for preparation of microspheres to encapsulate APIs. Moreover PLGA, PCL and PLA, diblock copolymers of lactide, ethylene glycol, L-lactide and ε-caprolactone, triblock co polymers of caprolactons, lactides and glycolides, have also been used to encapsulate APIs via o/w emulsion / solvent evaporation.<sup>(3)</sup>

Biodegradation rate of the microspheres is directly linked to its composition which in turn affects the release profiles of API. For instance as PGA, PLA and PCL have hydrolytic degradation rate in order of PGA > PLA >> PCL. PCL have excellent permeability in case of steroidal drugs but it shows slow biodegradation, in contrast, PLA and PGA had inferior permeability in case of steroidal drugs but it shows

homogenous biodegradation. It has been observed that microspheres of PLGA get degraded quicker and release of API is more rapid from the microspheres when hydrophilic glycolide component is increased in the system. The polymer's chirality, density of cross linking and loading of drugs in microspheres also influences the release profiles of API. Casein and chitosan microspheres shows slower release of API particularly when the amount of cross linking is increases significantly as it results in increased barrier density for drug diffusion, with reduction in the drug loading. Higher initial burst in microspheres has been observed when un-encapsulated drug is available in higher quantity on the surface of microspheres.<sup>(3)</sup>

The microsphere's size can be determined by the ratio of surface area to volume which gives an idea about the amount of surface accessible for releasing the APIs in the course of diffusion. Microspheres which are small in size, have higher ratio of surface area to volume and lesser diffusion path length and thus provides better API release and shorter duration. Microsphere's size inversely affects the effectiveness of the injectability, the bigger the size is, the more difficult they are to inject via needles. The Most favorable size range for effectiveness of injection is between 20 and 90  $\mu\text{m}$ . Concentration of polymers used for fabricating the microspheres have regulates the average size of microspheres. More the concentration of polymer is, higher is the organic phase viscosity in emulsion droplet and therefore the larger the average size which allow higher amount of APIs encapsulation into the microspheres. An additional important feature affecting release of API is molecular weight (MW) of the polymers used in construction of microspheres.<sup>(3)</sup>

## SELECTION OF METHOD OF PREPARATION OF MICROSPHERES

According to literature there are several methods of preparation for microspheres. In some cases, slight variation in basic methods is also reported. These variations in basic methods can produce numerous changes in final outcome. However, some of the basic techniques for microsphere preparation has been gathered from literature survey and are listed below

### Interfacial Polymerization Technique<sup>(4)</sup>

In this technique, two types of monomers are one is water soluble and the other monomer is oil soluble. These two monomers form a polymer on droplet surface. This method provides wide range of products to be encapsulated such as water immiscible liquids, solids and aqueous solutions.

However, this technique is mostly used for encapsulation of liquids in comparison to other products because polymerization is easily achieved when a liquid is used rather than a solid. There are few limitations or disadvantages of this process such as

- Reaction between active substance and reagents.
- Alteration in solubility of active substance
- Toxicity produced due to untreated monomers
- Degradation resulted by monomer reactions

High permeability of coating and fragility of microspheres

This technique can produce different type of microspheres such as microspheres having semi permeable or non permeable lipid membranes with aqueous core or release controlling coating with a solid core some of which are

mention below

### Water immiscible liquid core

In this monomer is dissolved in liquid water immiscible core. Normally used monomers in this scenario are isocyanate, acid chloride or some combination of both. A dispersing agent and a coreactant which is dispersed in an aqueous phase are used. Monomer solution is then added to this aqueous phase which results in polymerization at interface.

### Water miscible liquid core

Water in oil emulsion is formed with the help of an emulsifier when a solution of a hydrophilic liquid, is mixed in an oily phase. When reactant which is not soluble in water is added to this w/o emulsion, on the surface of liquid droplets a polymer membrane is created.

### Solid core

In this method, polymerization takes place spontaneously on solid surface. Solid core can be generated by vinyl monomer which helps in encapsulation and polymerization.

### Coacervation/ Phase Separation Technique<sup>(5)</sup>

Dutch scientist, Bungenburg de jong and Kruyt used term coacervation for the first time to describe the phase separation phenomenon in colloidal system. They observed that this phase separation or coacervation was the result of precipitation or flocculation of the colloidal material from solution and this coacervation occurred just before precipitation from solution. The term coacervate is constituted with amorphous liquid droplets of separated phase which is rich in colloids.

This coacervate is deposited around individual minute insoluble particles mixed in liquid which forms embryonic capsules. Appropriate gelling of this left coacervate consequences in nanoencapsulation. This method is subdivided into following types

### Aqueous Phase Separation

Only hydrophobic materials both in solid and liquid solid form can be encapsulated by this technique. In this process a wall material which is polymeric, is mixed in water and the water insoluble core material is mixed in above water phase. Encapsulation occurs when the nucleus material is precipitated and encases the hydrophobic nucleus material after adding of precipitating agent or decreased temperature or change of pH. This aqueous phase separation technique is also subdivided in to two types:

### Simple Coacervation

It can be achieved by the adding of a highly hydrophilic agent in the system e.g. alcohols and salts. The core material is dispersed in aqueous polymeric solution, in which insufficiency of water for hydrophilic colloid results deposition of coacervate around the core and transformed into gel and nanocapsule hardened Coacervates.

### Complex Coacervation

This process primarily depends on pH and involves neutralization of the charges of colloids. This is achieved by mixing two oppositely charged colloids together. This can be summarized in following steps:

- A hydrophilic colloid solution is prepared

- A second hydrophilic colloid solution is added to first hydrophilic colloid solution to induce coacervation
- Deposition occurs around the core
- Coacervates appears as gel and hardened structures

### Organic Phase Separation

Organic phase separation is just opposite of water phase separation technique. In this technique, the core is water miscible and the wall is hydrophobic in nature. In this, the water miscible material is enclosed in an oily solvent with a polymeric wall via addition of second polymeric material or non solvent. Polymeric concentration, temperature and amount of non solvent added will decide the quantity and state of polymer which is separated from the original solution.

### Organic Solvent Evaporation Technique <sup>(6)</sup>

The solvent evaporation technique involves emulsification process in which oily phase contains a dispersed polymer and water phase contains excess amount of dissolved/dispersed drug. Shape and particles size of formulated emulsion is affected by concentration of emulsifier present in aqueous phase. When the emulsion is formed in desired droplet size, stirring rate is decreased and evaporation of organic solvent is done under reduced atmospheric pressure at an optimum temperature. This results in solid polymeric microspheres entrapping the drug. These solid microspheres are recovered from suspension by different methods such as filtration, centrifugation or lyophilization. This method is subdivided into two parts:

- Single emulsion solvent evaporation
- Multiple emulsion solvent evaporation

### Spray Drying

Spray drying is generally applied in encapsulating sensitive subjects such as, essential oils, fragrances or vitamins. The solubility of drug in the polymer helps in deciding the internal structure of particles. Spray drying can be summarized as alteration of a feed from a liquefied condition such as dispersion, solution or paste, into a dehydrated particulate structure. This is done by inserting the feed into a hot gaseous drying medium as spray. It is a continuous one step processing operation in which four different phases are present.

- Feed atomization
- Spray and air mixing
- Solvent evaporation
- Separation of product

Sometimes aggregation of proteins and peptides is observed in microspheres creating a critical problem during preparation of dosage form. Selection of solvent in microsphere preparation may play a role <sup>(7)</sup>. Addition of additives in aqueous phase such as BSA <sup>(8)</sup>, Sugars and PEG<sup>(9)</sup> have been studied in microspheres preparation. These additives are released along with drug from microspheres and affect the stability of microspheres adversely.

To overcome the adverse effects of additives on release rate of microspheres Kand et al. suggested a new method in which microspheres of human growth hormones were initially prepared with dextrin and then encapsulated in PLGA <sup>(10)</sup>.

This W/O/W method reduced initial burst and optimized the release rate of drug from microspheres<sup>(11)</sup>.

However various problems are still not resolved with these methods like wide size distribution and poor repeatability.

Microspheres/Nanoparticles meant for parenteral use must be sterilized or prepared in aseptic environment and using sterile starting materials. The manufacturing process should also be checked continuously for safety of product <sup>(7)</sup>. Normally used terminal sterilization methods should not be used with microspheres/Nanoparticles containing proteins; peptides as gamma radiation or heat sterilization may degrade them and adversely affects the efficacy of product <sup>(12)</sup>. Similarly filtration cannot be used as sterilization method in case of microspheres as pore size of filter membrane is smaller than microspheres. Sterility testing should be as per pharmacopoeia standard for both external and internal aspects. The internal sterility is checked to verify the absence of microorganism inside the microspheres.

Internal sterility testing may be performed using mixing of culture media with a solvent which can dissolve microsphere and liberate the inner content<sup>(13)</sup>. Bacterial endotoxins may also be tested to check if endotoxins are well within the limits<sup>(14)</sup>.

Nath et al. used electro spraying method to prepare monodispersed particles containing PLGA in organic phase for preparation of simvastatin microspheres <sup>(15)</sup>. This method enhances encapsulation efficacy and lowered wide range particle size distribution of microspheres.

Recombinant human bone morphogenetic protein- 2 (rhBMP-2) loaded microspheres of PLGA were prepared by Zang et al. using coaxial electrospraying<sup>(16)</sup>. These microspheres were with narrow size distribution and during process of electro spraying there was no direct contact between drug and organic solvent. This process could protect drugs like proteins, genes and peptides which are unstable in organic solvent and lose their bioavailability. Uneven surface of these microspheres enhance cell adhesion and accelerates bone formation effect of drug.

Residual solvent effect is always a critical problem in quality control of microspheres as PLGA/PLA are normally dissolved in organic solvent like methylenedichloride and ethyl acetate as oil phase.

Supercritical carbon dioxide may be used as extracting agent to remove residual solvent from microspheres <sup>(17, 18)</sup>.

Recently near solvent free microspheres could be prepared with use of a new super critical emulsion extraction in a continuous process layout <sup>(19, 20)</sup>.

Emulsion solidification time is reduced by using a tower with counter current movement of emulsion and to improve encapsulation efficiency and reproducibility. This process is efficient for thermo labile drug due to mild operational temperature <sup>(21, 22)</sup>. This process is also used for light sensitive micro/nano devices <sup>(23)</sup>. Microspheres prepared by emulsification require mechanical stirrer to agitate two immiscible phases to reduce particle size of globules being easy process with low cost <sup>(24)</sup>. However in the end the size separation of microspheres is done by sieving method which reduces the yield and increases the cost. To improve the yield of desired sized microspheres Liu et al. used glass beads of 4-6 mm diameter in continuous phase. These glass beads were able to enhance homogeneous dispersion though mechanical stirring <sup>(25)</sup>. Through optimization of PLGA



concentration in solvent and with control of relative flow of aqueous and oil phase in mixing chamber Hung et al. prepared PLGA particles up to 70 nm<sup>(26)</sup>.

Uniform sized particles of PLGA may be prepared using premix membrane emulsification method with high yield. This method is able to produce microspheres of less than 8  $\mu$ m diameter<sup>(27)</sup>. Using premix membrane emulsification method through control of pressure difference across the membrane and its pore size, Qi et al. successfully prepared uniform size (20  $\mu$ m) microspheres of PLGA<sup>(28)</sup>. Hot melt extrusion method is used for preparation of granules, sustained release tablets, pellets and other traditional dosage forms<sup>(29)</sup>. In this process under optimized conditions drug and polymer mixture is extruded to prepare microspheres. PLGA/PLA microspheres are prepared by this method without using any organic solvent. As no organic solvent is evaporated from dosage forms hence no pores are developed during solidification and drug encapsulation is 100% theoretically<sup>(30)</sup>. Alorgan Inc. using hot extrusion method developed an implant containing dexamethasone with PLGA as intravitreal injection. The implant marketed with name as OZURDEX® for treatment of macular edema was approved by FDA in 2009<sup>(31)</sup>. However this method cannot be used for thermo labile drugs as high temperatures are used in hot melt extrusion method. Evonik®. Developed a method to prepare PLGA Microspheres named as FORMEZE. A packed bed column was used in the method for emulsification. In this process dispersing phase passes in continuous phase through pores between beads of 50-1000 $\mu$ m filled in the column. Emulsion is repeatedly passed through column to reduce the globule size<sup>(32)</sup> to 10-100  $\mu$ m. Controlled flow rate may be from 1 mL to 10<sup>5</sup> mL/min<sup>(29)</sup>.

Monodispersed PLGA/PLA microspheres or nano particles are prepared passing oil phase through the uniform pores of membrane into aqueous phase in membrane emulsification method to form uniform O/W emulsion. Liu et al. developed method to prepare w/o/w double emulsion using membrane emulsification method<sup>(33)</sup>. They control the release rate of drug through size of microsphere by selecting proper pore size membrane<sup>(34)</sup>. Method also provides higher drug entrapment efficiency in microspheres<sup>(35)</sup>. A modified method of direct membrane emulsification known as rotating membrane emulsification has also been used to prepare uniform sized polymer microspheres<sup>(36)</sup>. Liang et al. using rotating membrane emulsification method prepared PLGA microspheres of 100-1000 nm size. The prepared microspheres showed excellent therapeutic efficacy and good biosafety<sup>(37)</sup>. Size of microspheres may be precisely controlled with narrow size distribution with the help of precision particle fabrication by combining microfluidic technology with solvent extraction<sup>(38)</sup>.

In this method equipment with double nozzle is used in which oil phase is forced through inner nozzle in cylindrical jet form and aqueous phase at a higher rate from external nozzle. Frictional forces between oil phase jet and continuous phase generates droplets. The force of pumping both phases controls the size of globules<sup>(39)</sup>.

## LITERATURE REVIEW

This review is focused on microspheres which have been prepared using synthetic and natural biocompatible polymers. Also, it highlights the studies which involve preparation of microspheres intended for parenteral usage. This review also covers summary of different methods used for the preparations of microspheres as well as olanzapine as it is chosen drug for proposed research work.

One of the widely used biocompatible polymers is chitosan.

Microspheres of chitosan were prepared with polyurethane by emulsification method for cardio vascular drugs such as isosuprine hydrochloride and calcium dobesilate. Characterization of microspheres were carried out using FTIR and XRD which showed uniform dispersion in polymer matrix.<sup>(40)</sup>

Chitosan has also been used to prepare microspheres of different drugs used for oral administration. Inter polymer complexes were prepared using chitosan and cellulose acetate phthalate (CAP) by emulsification-solvent evaporation method. These microspheres were used for oral delivery of an antimetabolite drug, 5-FU categorized as antineoplastic agent. Release time of 5FU was extended by 12 hours using microsphere formulation.<sup>(41)</sup>

Redox polymerization technique was also used to prepare of microsphere of chitosan. These microspheres were cross linked with glutaraldehyde and were used to encapsulate enalapril maleate which is common drug for the treatment of hypertension.<sup>(42)</sup>

Chitosan was also used to prepare mucoadhesive microspheres for gastro-retentive delivery of acyclovir. Along with chitosan other mucoadhesive polymers were also used such as thiolate chitosan, Methocel K15M and carbopol 71G. These microspheres were prepared by emulsification-cross linking method.<sup>(43)</sup>

Small amount of chitosan blended in gelatin based microspheres showed prolong release of ceftiofour<sup>(44)</sup>. Gelatin is another polymer used to prepare microspheres. Gelatin has been used to convey heparin-binding growth factors for wound healing purposes.<sup>(45)</sup>

Carboxymethyl guar gum blended with gelatin resulted in microspheres which have semi-interpenetrating polymer network. These microspheres were prepared by emulsification method and was evaluated to determine controlled release of an antiasthmatic drug, theophylline<sup>(46)</sup>.

Gelatin microspheres of danofloxacin mesylate were prepared by emulsification-chemical cross linking technique.<sup>(47)</sup> Gentamycin loaded microspheres were prepared with b-tricalcium phosphate/gelatin for bone tissue engineering.<sup>(48)</sup>

Another polymer used to prepare microsphere is polycarbonate. It was used to encapsulate tetanus toxoid vaccine by modified emulsification-solvent evaporation technique<sup>(49)</sup>.

Bael fruit gum is also used to prepare microspheres of 5-FU by using as cross linking agent such as sodium trimeta phosphate in emulsification method. Encapsulating 5-FU was evaluated for anticancer efficacy against colon cancer<sup>(50)</sup>.

Poly(3-hydroxybutyrate) (PHB) is another polymer which was used in preparation of microspheres. The objective of these preparations was to study the controlled release characteristics of 6-mercaptopurine<sup>(51)</sup>.

Microsphere are also prepared by using eudragit L and S. Eudragit S and L were used to calculate the comparative input of microsphere and properties of drugs, specifically acid solubility, drug's molecular weight and microsphere size. A chain of nine drugs with diverse physiochemical properties were effectively encapsulated in Eudragit L and Eudragit S microspheres using a new emulsion solvent

evaporation procedure. This method resulted in spherical microparticles with a constricted size allotment (27-60 and 36-56 nm for Eudragit S and Eudragit L microspheres respectively)<sup>(52)</sup>

Another polymer used is ethyl cellulose which produces void microspheres as a novel dosage form with increased stomach retention time. These microspheres were prepared by solvent evaporation-diffusion method to produce a suspended drug delivery system for ranitidine.<sup>(53)</sup>

Most effective polymer being used today is PLGA. It has been used to prepare long acting injectable contraceptive. These PLGA microspheres provide contraceptive protection after one single injection for more than 3 months. 3 PLGA has been used to encapsulate leuprolide.<sup>(54)</sup>

The quality parameters of naltrexone microspheres based on the copolymer of lactic and glycolic acids (PLGA) were established as a function of the microencapsulation process parameters. The release profile of the developed naltrexone dosage form was found to coincide with that of the reference drug Vivitrol. The results were interesting scientifically and could be used to develop technology for producing generic Vivitrol.<sup>(55)</sup>

PLGA microspheres were used to characterize olanzapine on the foundation of in vitro behavior using dialysis. The goal of this formulation was to obtain an IVIV correlation<sup>(56)</sup>. Depot formulations of olanzapine loaded PLGA microsphere were also prepared and characterized. Findings clearly indicated that olanzapine PLGA microsphere can be used effectively to treat patients with varying mental conditions.<sup>(57)</sup>

Keru Zhang et al. reviewed the structure and structure dependent applications of PLGA/PEG polymers specially concentrating on micelles and hydrogels. They also studied drug loading in PLGA/PEG micelles and reported its drug release profile<sup>(58)</sup>. Farshad Ramzani et al. reported that for low molecular weight drugs microspheres are efficient controlled drug delivery systems. Emulsification with solvent extraction method reported to be with high encapsulation efficiency for hydrophobic small molecules. However Hydrophilic or amphiphilic small molecular may have low encapsulation as drug is partitioned between polymeric and external phase.<sup>(59)</sup>

Tianshi Feng et al. Developed low density highly porous microspheres of PLGA for pulmonary drug delivery and studied synergistic release of paclitaxel and doxorubicin simultaneously in these microspheres<sup>(60)</sup>. They found that for maximum therapeutic effects there should be higher ratio 5:1 of doxorubicin to paclitaxel. Release of paclitaxel and doxorubicin from double; layered microspheres, was reported in a similar study by Wei Li Lee et al. along with effects of loading two drugs in one single formulation and layer thickness on release rate. Microspheres prepared with PLGA having double layer loaded with two drugs subjected to drug release kinetics. Spheroids of MCF-7 cells were used to study the comparative anticancer effects of single layer and double layer microspheres with single drug and dual drug loading<sup>(61)</sup>. It has been reported that implants of glucose biosensors have relatively short life as these are reacted as foreign body which is a major cause of dysfunction. But if coating of a biocompatible polymer is applied on implants the problem is resolved<sup>(62)</sup>. Bing GuYanWang and Diane J. Burgess studied effect of PVA hydrogel coating on release of dexamethasone from PLGA microspheres. They used mixture of low molecular weight (25 KDa) and high molecular weights (113 KDa) PLGA at different mass ratio to achieve long term drug

release. It was concluded that use of polymer blend with PVA hydrogel coating enhances efficacy of biosensor up to 4.5 months against foreign body reactions<sup>(63)</sup>. During formulation of protein drugs in microspheres/microencapsules wide distribution size and poor reproducibility has been observed along with deactivation of proteins, reducing efficacy of formulation. Sonication and mechanical stirring during common process may denature protein molecules. However use of member emulsification method has great advantages over conventional method of having uniform microspheres size and higher entrapment for drug. The release rate of drug can be controlled by optimizing thickness of coating of encapsulating material. Guang hui Ma in a study of preparation of microcapsule reported that use of protein drug powder instead of solution and using hydrophilic PELA as coating material with self solidification process prepared microcapsules were of uniform size and were able to maintain blood level of growth hormones (rhGH) for two months with single dose<sup>(64)</sup>.

Hao Wang et al. prepared chitosan microspheres loaded with docetaxel for lung targeted formulation. Microspheres were prepared using glutaraldehyde cross linking in water in oil emulsion. They found that this method is superior to conventional method in terms of uniform particle size distribution, morphological characters drug loading and *in vitro* release of drug<sup>(65)</sup>. Imatinib loaded PLGA microsphere for sustain release were prepared by Nostrum et al. with high loading efficiency with sustain release of drug over a long period. Imatinib loaded PLGA microspheres were prepared by Nostrum et al. using dichloromethane as volatile solvent. Prepared microphese were of 6-20  $\mu\text{m}$  size with smooth non porous surface using a double emulsion W/O/W method<sup>(66)</sup>. Drug loading efficiency was found to be pH dependent (water phase). Microspheres were able to release drug for three months through diffusion of polymer matrix and erosion of polymer.

Donepezil encapsulated microspheres were prepared by Wenjia Guo et al. for sustain release of drug for one week. PLGA was used for encapsulation material and solvent evaporation technique was used for the preparation of O/W emulsion<sup>(67)</sup>. Microspheres with 30  $\mu\text{m}$  mean diameter and  $15.92 \pm 0.31\%$  drug loading efficiency were prepared. Differential scanning calorimetry and X ray diffraction revealed non porous surface and amorphous form of drug in the microspheres. Target oriented magnetic PLGA microspheres for chemotherapeutic therapy of cancer were prepared using doxorubicin as anticancer drug. Alternating current magnetic field was used to control the release of drug from microspheres having 28.3% Wt of Y-Fe<sub>2</sub>O<sub>3</sub> (Ferric oxide). It was observed that drug release from ACMF exposed microspheres was seven times higher to that not exposed to magnetic field.<sup>(68)</sup>

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